REMARKS

Applicants thank the Examiner and Supervisory Examiner for the personal interview of October 22, 2009, where the obviousness rejection was mainly discussed.

After entry of this amendment, claims 1-30 are pending, of which claims 5-9, 11-26, 28, and 29 are withdrawn. Claim 2 has been amended without prejudice or disclaimer to cancel non-elected part b. Part b of claim 2 corresponds to new claim 30. No new matter has been added.

The amendments to the title and the abstract find support in the original title and in the specification, for example, at page 5, lines 12-30. No new matter has been added.

Should linking claims 1, 3, 4, and 27 be found allowable then the linked claims are requested to be rejoined as well as any claim which depends from or includes all the limitations of an allowable claim. MPEP §§ 809 and 821.04.

Claim Objections

The Examiner requested that part b of claim 2 be deleted for being directed to non-elected subject matter. In light of the amendments, the objection is rendered moot.

The Examiner additionally objects to claim 2 for allegedly failing to limit the subject matter of the claim from which it depends. Applicants respectfully disagree. Parts a and b of claim 2 are presented in the alternative. Accordingly claim 2 refers to either part a ***or*** part b, each part providing an example of the way the combination referred to in claim 1 can be broken. Thus part a further limits claim 1, and part b further limits claim 1. Nonetheless in order to expedite prosecution, the claims have been amended without prejudice or disclaimer, where part b of claim 2 has been deleted from claim 2 and presented in new dependent claim 30. Accordingly the objection is believed to be rendered moot.

Reconsideration and withdrawal of the claim objections is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3, 4, 10, and 27 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being incomplete. Applicants respectfully disagree.

The Examiner alleges that the claims omit an essential step and that such an omission amounts to a gap between the steps referring to MPEP § 2172.01. However, pursuant to MPEP § 2172.01 for a proper rejection based on omitting an essential or critical feature, the step or feature must be described in the specification by applicant as necessary or essential. Additionally as explained in MPEP § 2172.01, "it is not essential to a patentable combination that there be interdependency between the elements of the claimed device or that all the elements operate concurrently toward the desired result." *Ex parte Nolden*, 149 USPQ 378, 380 (Bd. Pat. App. 1965); see also *Ex parte Huber*, 148 USPQ 447, 448-49 (Bd. Pat. App. 1965) (A claim does not necessarily fail to comply with 35 U.S.C. 112, second paragraph where the various elements do not function simultaneously, are not directly functionally related, do not directly intercooperate, and/or serve independent purposes.).

Claim 1 includes a step of breaking the combination between the expression cassettes. However, the way in which the combination is broken is not described in the specification as essential. Rather the specification describes generally how the combination can be broken and that the combination can be broken by various methods, for example, at page 29, lines 10-14. Various methods on how the combination can be broken are also shown in the Figures, for example, in Figures 8-10. Because the way in which the combination is broken is not described in the specification by applicant as necessary or essential as would be required for a proper rejection, the rejection based on omitting an essential step is improper.

Additionally, one of skill in the art would know of additional methods for breaking the combination, for example, the combination can be broken by segregation of the two expression cassettes which can be on separate DNA constructs co-transformed by using two expression cassettes comprised on two independent vectors which can be delivered by two independent *Agrobacterium* lines, or the two expression cassettes can be comprised on two independent vectors which may be delivered in one *Agrobacterium* line, or the two expression cassettes can

be delivered on one vector in independent T-DNAs. Thus, the way in which the combination is broken is not essential since whichever method is chosen, the result is similar and a skilled person is aware of various different methods on how this can be achieved as also described in the specification.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-4, 10, and 27 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

The Examiner alleges that Applicants do not describe any D-amino acids other than D-alanine and D-serine that can function as required for compound "X" or any D-amino acids other than D-isoleucine and D-valine that can function as required for compound "M". The Examiner further alleges that Applicants do not describe any analogues, derivatives and mimetics of D-amino acids that maintain the functional activity of the compounds. The Examiner additionally contends that Applicants fail to describe a representative number of D-amino acid structures that can function as required for compound X and compound M and fail to describe structural features common to members of the claimed genus of D-amino acid structures. Applicants strongly disagree.

The specification describes possible embodiments for compound X and compound M, for example, at page 7, lines 28-39, which provides:

> In another preferred embodiment the first (phytotoxic) compound X is preferably comprising a D-amino acid structure selected from the group consisting of D-tryptophane, D-histidine, D-arginine, D-threonine, D-methionine, D-serine, and D-alanine; more preferably D-alanine, D-serine, and derivatives thereof. Most preferably, X is comprising and/or consisting of D-alanine, D-Serine, or derivatives thereof.
>
> In another preferred embodiment the second (non-phytotoxic, but metabolizable into phytotoxic) compound M is preferably comprising a D-amino acid structure selected from the group consisting of D-isoleucine, D-valine, D-asparagine, D-leucine, D-lysine, D-proline, and D-glutamine; more preferably D-isoleucine, D-valine, and derivatives thereof. Most preferably, M is comprising and/or consisting of D-isoleucine, D-valine, or derivatives thereof.

Also see specification, for example, at page 31, lines 22-40.

Additionally, Figure 3 illustrates various D-amino acids which can be used as compound M and as compound X based on their effect on wild-type plants. Thus, contrary to the Examiner's assertion, the specification clearly describes more than just D-alanine and D-serine for compound X and more than just D-isoleucine and D-valine for compound M.

The specification also describes various D-amino acid structures, for example at page 40, lines 33-42, which provides:

> For example, the term "D-phenylalanine structure" is intended to include D-phenylalanine as well as D-pyridylalanine and D-homophenylalanine. The term "D-leucine structure" is intended to include D-leucine, as well as substitution with D-valine or other natural or non-natural amino acid having an aliphatic side chain, such as D-norleucine. The term "D-valine structure" is intended to include D-valine, as well as substitution with D-leucine or other natural or non-natural amino acid having an aliphatic side chain.

The specification additionally describes various derivatives and modifications of D-amino acids such as their side chains, for example, at page 41 line 1 through page 43 line 12. In addition, the specification provides references to indicate that such D-amino acid structures would be known to one skilled in the art. See specification, for example, at page 41, lines 26-35. A patent need not disclose what is well known to those skilled in the art and preferably ***omits that which is well known to those skilled and already available*** to the public. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991) (emphasis added).

The Examiner further concludes that "Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*." (Office Action dated July 28, 2009, page 9). Applicants strongly disagree with the Examiner's characterization and interpretation. First, the test set forth in *Eli Lilly* is not a two prong test but rather sets forth alternatives, any one of the alternatives may be adequate to meet the written description requirement. *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) ("A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus ***or*** of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." (emphasis added)). As explained above, Applicants have

described a representative number of D-amino acids and D-amino acid structures and accordingly it is respectfully submitted that the specification provides adequate written description for the present claims under the applicable *Eli Lilly* standard.

The Examiner alleges that the only D-amino acids described for compound X and for compound M are those found in certain examples (Office Action, for example at page 10). However, as explained by the Board in *Ex parte Stockert*, Appeal 2007-0543, (Bd.Pat.App. & Interf., March 23, 2007), where the Board reversed the written description rejection, "[A]pplicants have some flexibility in the 'mode selected for compliance' with the written description requirement" (*University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 928, 69 USPQ2d 1886, 1896 (Fed. Cir. 2004)), and ***it is well settled that actual reduction to practice is not necessary to satisfy the requirement*** (*Id.* at 926, 69 USPQ2d at 1894). See also *In re Angstadt*, 537 F.2d 498 (CCPA 1976) (holding that there has never been a requirement that every species encompassed by a claim must be disclosed or exemplified). Moreover, Applicants have described numerous other D-amino acids for compound X and compound M as explained above.

Furthermore, the Examiner "has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976); *see also* MPEP § 2163. The Examiner concludes that D-amino acid structures were allegedly not in possession of the applicant at the time of filing. (Office Action, pages 9-10). However, the Examiner has not presented the requisite evidence or reasons for such a statement especially given that the specification provides description of numerous D-amino acids and D-amino acid structures for compound X and compound M in addition to references indicating that such compounds would be known to one skilled in the art as explained above.

Thus, contrary to the Examiner assertion, because the specification does describe a representative number of D-amino acids and D-amino acid structures which can be used as compound X and compound M as also illustrated in the figures (for example, Figure 3), the specification does provide adequate the written description. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1-4, 10, and 27 were rejected under 35 U.S.C. 103(a) as allegedly being obvious over Signer *et al.* (WO 01/96583; hereinafter "Signer) in view of Nasholm *et al.* (WO 03/060133; hereinafter "Nasholm") and taken with the evidence of Stougaard and the evidence of Boeke *et al.* (hereinafter "Boeke"). Applicants respectfully traverse.

The claims are non-obvious over Signer in view of Nasholm and taken with the evidence of Stougaard and the evidence of Boeke for the following reasons.

1. The References Do Not Teach Or Suggest All The Claim Limitations.

The Examiner bears the initial burden of establishing *prima facie* obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See *In re Lowry*, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994).

The Examiner contends that Signer teaches a method of generating a transgenic plant that utilizes both a positive and a negative selection marker in order to remove the selection markers from the resulting transgenic plants. (Office Action dated July 28, 2009, page 11). However, the construct of Signer requires two different selectable markers. (Signer, page 2, paragraph [0007], Examples 1-3, claims 1-3, 10-16, Figure 1). The construct taught in Signer uses an NPT gene as the positive selectable marker and the *CodA* gene as the negative selectable marker. Furthermore, the positive selection medium used in Signer acts with the NPT gene, the positive selectable marker, and the negative selection medium acts with the *CodA* gene, the negative selectable marker. Thus, the two selection media act with two different types of selectable markers. In contrast to Signer, the present claims relate to the use of only one enzyme, D-amino acid oxidase, as a selectable marker for both positive and negative selection in one construct as a dual-functional marker for eliminating marker sequences from transgenic plants. Further in contrast to Signer, the two selection compounds of the present claims (compound X and M) act with only one selectable marker (D-amino acid oxidase).

The Examiner acknowledges that Signer does not teach a sequence encoding a D-amino oxidase gene for use as either a positive or negative selectable marker and relies on Nasholm for

allegedly teaching that D-amino acids can be used for selection of transgenic plants expressing D-amino acid oxidase as a positive selection marker or a negative selection marker. However, Nasholm does not teach or disclose the use of D-amino acid oxidase as a dual-functional selection marker for eliminating marker sequences from transgenic plants.

The Examiner concludes that it would be obvious and within the scope of one or ordinary skill to modify the teaching of Signer to utilize a D-amino acid oxidase as taught by Nasholm and one would be motivated to do so because Nasholm allegedly taught that "one transgene could be useful as both a positive and a negative selection marker" and "one would only require one transgene rather than two separate selectable marker genes." (Office Action dated July 28, 2009, pages 12-13). The Examiner further contends that this concept was generally known in the art citing to Stougaard and Boeke. Applicants strongly disagree with the Examiner's interpretation and conclusions.

Stougaard discloses that *CodA* can be used as either a negative selectable marker or a positive selectable marker. Although *CodA* was known as a marker that could be used as either a positive or a negative selectable marker, for the production of marker-free plants, rather Signer teaches that two distinct selectable markers are necessary even if one of these is a potential dual functional marker. Moreover nothing in Signer teaches or suggests using a construct which would be equivalent to eliminating the positive selectable marker used, *i.e.* the NPT gene, and only using the negative selectable marker *CodA* which was known as a marker that could be used as either a positive or a negative selectable marker. Contrary to the Examiner's assertion, nothing in Stougaard discloses the use of *CodA* as a dual-functional selection marker in one construct. Contrary to the Examiner's assertion, nothing in Signer discloses that one transgene rather than two separate selectable marker genes can be used for marker excision. Contrary to the Examiner's assertion, nothing in Signer discloses eliminating one of the selectable markers and only using the other which was known as a marker that could be used as either a positive or a negative selectable marker.

Regarding Boeke, Applicants fail to see the relevancy of this reference since it relates to yeast systems and not to transgenic plants. Additionally, Boeke describes using the *URA3* gene in their yeast system which is totally different than the *CodA* gene described in Signer and

Stougaard, the NPT gene of Signer, or the D-amino acid oxidase of Nasholm. Accordingly Boeke is inapplicable.

Therefore, none of the references cited by the Examiner, alone or in combination, teach or disclose the use of a single selectable marker such as D-amino acid oxidase as a dual-functional selection marker for eliminating marker sequences from transgenic plants. Because the references cited by the Examiner do not disclose or suggest all the claim limitations, a *prima facie* case of obviousness has not been established. For this reason alone, the obviousness rejection should be withdrawn.

2) The References Teach Away From The Claimed Invention.

It is well established that under 35 U.S.C. § 103 the Examiner must consider the reference as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); see also *KSR*, 127 S. Ct. at 1740; MPEP § 2141.03 (VI).

When considered as a whole, Signer teaches away from the claimed invention. Stougaard teaches that *CodA* can be used as either a positive or a negative selection marker. However, for the production of marker-free plants, Signer requires the use of at least two distinct markers, one used as a positive selectable marker (an NPT gene), and the other as the negative selectable marker (the *CodA* gene). The proposed modification suggested by the Examiner would be equivalent to eliminating the positive selectable marker used, *i.e.* the NPT gene, from the construct of Signer and only using the negative selectable marker *CodA* which was known as a marker that could be used as either a positive or a negative selectable marker. Although *CodA* was known as a marker that could be used as either a positive or a negative selectable marker as taught by Stougaard, for the production of marker-free plants, Signer teaches that two distinct selectable markers are necessary even if one of these is a potential dual functional marker. Nothing in Signer suggests the elimination of the positive selectable marker used to be left with one marker that is a potential dual functional marker. The method of Signer also teaches that each of the selection media act with a different selectable marker. Accordingly, Signer leads

away from the claimed invention which relates to using a single transgene and different selection compounds that would act with a single dual functional marker.

Accordingly, a *prima facie* case of obviousness has not established for this additional reason.

3) The References Do Not Provide Any Suggestion Or Motivation For One Skilled In The Art To Modify The Method Of Signer And Teach Away From The Modification.

The Examiner alleges that it would be obvious and within the scope of one of ordinary skill to modify the teaching of Signer to utilize the D-amino acid oxidase of Nasholm and that one would be motivated to do so because Nasholm allegedly teaches that D-amino acid oxidase can be useful as both a positive and a negative selection marker and one would only require one transgene rather than two. However, contrary to the Examiner's assertion, one of the selectable markers in the Signer construct, *i.e. CodA*, was already known as a marker that could be used as either a positive or a negative selectable marker as taught by Stougaard, and yet Signer till required the use of two selectable markers for marker excision. Because Signer required the use of two selectable markers for marker excision even when one of them was known to be a marker that could be used as either a positive or a negative selectable marker, from the teaching of Signer one skilled in the art would use a construct with at least two distinct selectable marker genes for marker excision. The proposed modification suggested by the Examiner would be equivalent to eliminating the positive selection marker used in the construct of Signer and only using the negative selection marker as both a positive and a negative selectable marker. However, contrary to the Examiner's assertion, nothing in Signer or Nasholm leads one skilled in the art to eliminate one of the selectable markers or to use a single transgene and rather leads one skilled in the art to use two distinct selectable markers for marker excision.

"[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Nothing in the references would have prompted one of ordinary skill in the art to eliminate the positive selectable marker used in the Signer construct or to use a single transgene for marker excision in the way the claimed new

invention does. It is only from the teaching of the present specification that one would be guided to use a single transgene as a dual functional marker in one construct for marker excision which is tantamount to impermissible hindsight, which the Court in *KSR* guards against. *Id.* at 1741 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight."). Accordingly, a *prima facie* case of obviousness has not established for this additional reason.

4) The Modification Suggested By The Examiner Requires A Substantial Reconstruction And Redesign Of The Construct Being Modified Changing The Principle Under Which The Method Being Modified Operates.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (The court reversed the obviousness rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.). MPEP § 2143.01 VI.

Assuming *arguendo*, Signer, Nasholm, and Stougaard were combinable, the proposed modification to Signer suggested by the Examiner requires a "substantial reconstruction and redesign" of elements and changes the principle under which Signer operates.

Signer describes using a construct comprising direct repeats of the gene of interest which flank at least two different types of selectable markers. (Signer, page 2, paragraphs [0006]). Signer provides the following general formula to depict the construct: GI-PS-NS-GI or GI-NS-PS-GI, where GI is the gene of interest, PS is the positive selectable marker gene, and NS is the negative selectable marker gene. (Signer, page 2, paragraphs [0006]-[0007]). Signer also discloses the positive selectable marker as a NPT gene and the negative selectable marker as the *CodA* gene (Signer pages 13-16, Examples 1-3). Signer further discloses that the positive selection medium comprises kanamycin which acts upon the positive selectable marker, *i.e.* the

NPT gene, and that the negative selection medium comprises 5-fluorocystosine, which acts with the negative selectable marker, *i.e.* the *CodA* gene (Signer, for example, at pages 13-16, Examples 1-3). Thus, the method described by Signer requires two different types of selectable markers and two different selection media comprising compounds where each of the selection media acts with a different selectable marker.

The modification suggested by the Examiner requires a major reconstruction and redesign of the construct and method of Signer from a construct with two different types of selectable markers to a construct with one transgene. As one option the major reconstruction or redesign would require eliminating both, *i.e.* the NPT gene and the *CodA* gene, and replacing these two genes with a construct with one single selectable marker gene which could be used as both a positive and a negative selection marker. As another option the major reconstruction or redesign would require eliminating one of the selectable markers, *i.e.* the NPT gene, from the Signer construct and leaving the *CodA* gene known as a marker which could be used as a positive or a negative selection marker by the teaching of Stougaard, then substituting the *CodA* gene. However, either option for redesigning the construct would change the basic principle under which the Signer construct was designed to operate. Assuming *arguendo* that the NPT gene was eliminated and only *CodA* remained in the construct or that a single transgene was in the construct, the selection media taught by Signer would not operate for its intended purpose since these are designed to each act on separate different selectable markers with only one designed to act with the *CodA* gene and none designed to act on a single selectable marker as both a positive selection media and a negative selection media.

Assuming *arguendo* that there was a reason to eliminate the positive selectable marker from the construct of Signer or that there was a reason to substitute a construct comprising two selectable markers with one of them being a selectable marker which could be used as a positive selectable marker or a negative selectable marker, eliminating one of the selectable markers or substituting the construct of Signer with a construct with a single transgene which could be used as a positive selectable marker and a negative selectable marker would change the basic principle under which the Signer process was designed to operate and as such the teachings of the references are not sufficient to render the claims *prima facie* obvious.

5) Even With the Suggested Modification, One Skilled In The Art Would Not Arrive At The Claimed Invention.

Assuming *arguendo* that Signer and Nasholm were combinable, the substitution of D-amino acid oxidase into the method of Signer would result in a different method than that claimed. As explained above, the construct and method of Signer use two different selectable markers, an NPT gene and the *CodA* gene. The Examiner alleges that Stougaard teaches that the *CodA* gene can be used as either a positive or a negative selection marker and that Nasholm teaches that D-amino acid oxidase can be used as a positive or a negative selection marker. Substituting these two potential dual functional marker genes, one skilled in the art would still not arrive at the claim invention, since the resulting construct would still comprise two different selectable markers, the NPT gene and the dual functional selectable marker.

Assuming *arguendo* that there was a reason to eliminate the positive selectable marker from the construct of Signer or that there was a reason to substitute a construct comprising two selectable markers with a construct with one dual functional selectable marker and these modification were made, one skilled in the art would still not arrive at the claim invention, since the two different selection media would still each act on separate different selectable markers with only one able to act with the *CodA* gene and none of the two different selection media able to act on a single selectable marker, *i.e.* as a positive selection media and as a negative selection media on the same selectable marker.

Because the modification suggested by the Examiner does not arrive at the claimed method, a *prima facie* case of obviousness has not been established for this additional reason.

For at least these reasons, Signer, Nasholm, Stougaard, and Boeke, alone or in combination, do not render obvious the subject matter of the independent claims or the claims dependent therefrom. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious).

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

Applicants are submitting their response within the three-month response period for response to and including October 28, 2009. No fee is believed due. However if a fee is due, the Director is hereby authorized to charge or credit any overpayment to our Deposit Account No. 03-2775, under Order No. 13987-00022-US from which the undersigned is authorized to draw.

Respectfully submitted,

By _____

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